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CORRELATION BETWEEN HISTOPATHOLOGICAL FEATURES AND CLINICAL PRESENTATION OF ORAL SQUAMOUS CELL CARCINOMA

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Abstract

Background: Oral squamous cell carcinoma (OSCC) is one of the most common malignancies in South Asia, with high morbidity and mortality. Despite its prevalence, limited data are available in Pakistan correlating clinical features with histopathological characteristics.

Objective: To evaluate the correlation between histopathological features and clinical presentation of oral squamous cell carcinoma

Methodology: This cross-sectional study was conducted over a period of one year 1st July2024 to 30th June 2025. A total of 246 patients were included. Demographic, clinical, and risk factor data were recorded through structured proformas. Data were analyzed using SPSS v. 25. Associations between clinical and histopathological parameters were assessed using the chi-square test, with $p < 0.05$ considered significant.

Results: The mean age was 51.7 years, with most patients aged 40–59 years (56.1%) and predominantly male (63.4%). Betel quid chewing (52.0%) and smoking (47.2%) were the most common risk factors. Buccal mucosa (41.5%) and tongue (30.9%) were the most affected sites. Histologically, 45.5% were moderately differentiated, 43.9% had infiltrative invasion, and 26.0% showed perineural invasion. Clinical stage and nodal status showed a significant association with tumor grade ($p < 0.05$).

Conclusion: OSCC in Pakistan predominantly presents in middle-aged males with strong links to tobacco and betel quid use. The late-stage diagnosis and aggressive histopathological features highlight the need for early detection strategies and preventive public health interventions.

Keywords: Oral squamous cell carcinoma; Risk factors; Histopathology; Betel quid; Tobacco; Pakistan

Introduction

Oral squamous cell carcinoma (OSCC) is among the most prevalent malignancies of the head and neck region and represents a significant global health burden.[1] OSCC arises from the epithelial lining of the oral mucosa, and despite advances in diagnostic modalities and treatment, the prognosis remains poor in many settings. The disease is particularly challenging because many patients present at an advanced stage, the patterns of disease vary according to risk factors such as tobacco, betel quid, areca nut, and other habits, and histopathological features such as degree of differentiation, pattern of invasion, and variant sub-types influence both clinical behavior and outcome.[2]

Epidemiologically, Pakistan bears a disproportionately high burden of OSCC. Various studies have demonstrated that OSCC is among the top ten most common cancers in the country, with high incidence especially in regions where smokeless tobacco or areca nut chewing are common. A study of 138 patients in Karachi, the mean age of patients was 48.6 years, most were male, and a majority presented with well-differentiated carcinoma. Histopathologically, a study showed that moderately differentiated OSCC tends to be the most common grade, with well-differentiated cases also substantial, and poorly differentiated variants less common but associated with more aggressive disease.[3-5]

Clinically, the presentation of OSCC in Pakistan is influenced by socio-demographic factors, stage at presentation, risk-habits, tumor site and size, and histopathological grades in tobacco users more often involve the buccal mucosa and tend to be diagnosed later. Moreover, clinical stage correlates with histopathological features: advanced TNM stage, lymph node involvement, poorer differentiation, deeper invasion, and less favorable variants are linked with worse prognosis.[6, 7]Early-stage tumors generally have better outcomes, underscoring the clinical importance of early detection and characterization. However, many studies in Pakistan report that patients often present with late-stage disease, reflecting barriers in access, awareness, or screening.[8, 9]

Despite existing literature, gaps remain in understanding how specific histopathological features correspond with clinical presentation in Pakistani patient populations. Such correlation is important for prognostication, guiding treatment strategies, and potentially for public health interventions aimed at early diagnosis. Given the high morbidity and mortality of OSCC in Pakistan, and the variation in both clinical presentation and histopathology observed, this study is warranted to define better how microscopic features correspond to clinical parameters among Pakistani patients. This study aimed to investigate the correlation between histopathological features (including histological grade, variant, pattern of invasion) and clinical presentation (age, gender, site of tumor, stage at diagnosis, risk habits, duration of symptoms) of OSCC in a sample of Pakistani patients. The present study aimed to evaluate the correlation between histopathological features and clinical presentation of oral squamous cell carcinoma.

Methodology

This study was designed as a cross-sectional analytical study to explore the correlation between histopathological features and clinical presentation of oral squamous cell carcinoma (OSCC) patients. It was conducted in the Islamabad. The study was carried out over a period of six months from 1st July 2024 to 30th June 2025.

The sample size was calculated using OpenEpi (Version 3.01), considering an estimated prevalence of OSCC of 10%-16% in Pakistan, a 95% confidence interval, and a 5% margin of error.[10] The minimum sample size was calculated as 246 patients.

A non-probability consecutive sampling technique was employed. Patients of either gender, aged 18 years or above, with histopathologically confirmed OSCC were included in the study. Only those presenting with primary tumors of the oral cavity and who provided informed consent were enrolled. Patients with recurrent OSCC, other histological subtypes of oral malignancies such as salivary gland tumors or lymphomas, and those with incomplete medical records or inadequate biopsy specimens were excluded. Additionally, patients suffering from systemic comorbidities

known to significantly alter histopathological architecture, such as immunodeficiency disorders, were not included.

The data collection procedure involved several steps. Eligible patients were first identified in the Oral & Maxillofacial Surgery Department. The objectives of the study were explained, and informed consent was obtained. Demographic and clinical data were collected using a structured proforma, which included variables such as age, gender, residence, and socioeconomic status. Clinical characteristics were documented, including risk factors such as smoking, smokeless tobacco, betel quid, and areca nut use. The site of the lesion, duration of symptoms, mode of clinical presentation (such as ulcer, mass, pain, or dysphagia), and TNM staging at the time of diagnosis were also recorded. Clinical examination was performed to confirm lesion characteristics and assess regional lymph node involvement.

Histopathological data were obtained from biopsy specimens, which were fixed in 10% buffered formalin and processed according to standard protocols. Sections were stained with hematoxylin and eosin (H&E) and evaluated under light microscopy. The histopathological features assessed included histological grade (well-differentiated, moderately differentiated, and poorly differentiated carcinoma), pattern of invasion, depth of invasion, tumor thickness, and the presence of keratin pearls, mitotic activity, and perineural invasion.

To reduce interobserver bias, all slides were examined independently by two experienced histopathologists, and any discrepancies were resolved through consensus. Clinical and histopathological data were then cross-checked for accuracy and completeness before being entered into a computerized database for statistical analysis.

Data analysis was conducted using the Statistical Package for Social Sciences (SPSS), version 25.0. Descriptive statistics, including means and standard deviations for continuous variables and frequencies and percentages for categorical variables, were calculated. Associations between clinical parameters (age, gender, lesion site, clinical stage, and risk factors) and histopathological features (grade, pattern of invasion, and depth of invasion) were assessed using the chi-square (χ^2) test, and a p-value of less than 0.05 was considered statistically significant.

Results

Among the 246 patients with OSCC, more than half (56.1%) were between 40 and 59 years of age, while 26.8% were aged 60 years or above, and 17.1% were younger than 40 years. The mean age of patients was 51.7 years. A male predominance was observed, with 63.4% males compared to 36.6% females. The majority of patients resided in urban areas (60.2%), whereas 39.8% belonged to rural regions. Regarding socioeconomic status, most patients were from the low socioeconomic group (53.7%), followed by the middle (37.4%) and high socioeconomic groups (8.9%). (Table 1)

Table 1. Demographic Characteristics of Patients with OSCC (n = 246)

Variable	**Categories**	**n (%)**
Age (years)	**< 40**	42 (17.1)
	40–59	138 (56.1)
	≥ 60	66 (26.8)
Mean ± SD	51.7 ± 11.8	
Gender	**Male**	156 (63.4)
	Female	90 (36.6)
Residence	**Urban**	148 (60.2)
	Rural	98 (39.8)
Socioeconomic status	**Low**	132 (53.7)
	Middle	92 (37.4)
	High	22 (8.9)

Nearly half of the patients (47.2%) reported a history of smoking, while 37.4% used smokeless tobacco. Betel quid chewing was the most common risk factor, observed in 52.0% of patients, whereas 29.3% reported areca nut chewing. (Table 2)

Table 2. Risk Factors Associated with OSCC of study participants (n=246)

Risk Factor	Present n (%)	Absent n (%)
Smoking	116 (47.2)	130 (52.8)
Smokeless tobacco	92 (37.4)	154 (62.6)
Betel quid chewing	128 (52.0)	118 (48.0)
Areca nut chewing	72 (29.3)	174 (70.7)

Regarding clinical presentation, the buccal mucosa was the most common site of lesion (41.5%), followed by the tongue (30.9%), lip (11.4%), gingiva/alveolus (9.7%), and floor of mouth (6.5%). The duration of symptoms was between 3 and 6 months in most patients (44.7%), whereas 33.3% presented after more than 6 months and 22.0% within 3 months.

Ulcerative lesions were the predominant mode of presentation (50.4%), followed by exophytic masses (33.3%) and pain or dysphagia (16.3%). In terms of staging, 17.1% of cases were diagnosed at stage I, 26.8% at stage II, 29.3% at stage III, and 26.8% at stage IV. Lymph node involvement was noted in 38.2% of patients, while 61.8% had no nodal disease. (Table 3)

Table 3. Clinical Presentation of OSCC of study participants (n=246)

Clinical Variable	Categories	n (%)
Site of lesion	**Buccal mucosa**	102 (41.5)
	Tongue	76 (30.9)
	Lip	28 (11.4)
	Floor of mouth	16 (6.5)
	Gingiva/Alveolus	24 (9.7)
Duration of symptoms	**< 3 months**	54 (22.0)
	3–6 months	110 (44.7)
	> 6 months	82 (33.3)
Mode of presentation	**Ulcer**	124 (50.4)
	Exophytic mass	82 (33.3)
	Pain/Dysphagia	40 (16.3)
TNM stage	**I**	42 (17.1)
	II	66 (26.8)
	III	72 (29.3)
	IV	66 (26.8)
Lymph node involvement	**Present**	94 (38.2)
	Absent	152 (61.8)

Histopathological evaluation revealed that 39.8% of tumors were well differentiated, 45.5% were moderately differentiated, and 14.7% were poorly differentiated. More than half of the cases (56.1%) showed an infiltrative pattern of invasion, whereas 43.9% displayed a pushing pattern.

Depth of invasion exceeded 10 mm in 43.9% of cases, was 5–10 mm in 39.0%, and less than 5 mm in 17.1%. Similarly, tumor thickness was 4–10 mm in 42.3% of patients, greater than 10 mm in 35.7%, and less than 4 mm in 22.0%. Keratin pearls were identified in 57.7% of cases, while absent in 42.3%. Perineural invasion was present in 26.0% of tumors and absent in 74.0%. (Table 4)

Table 4. Histopathological Features of OSCC of study participants (n=246)

Feature	Categories	n (%)
Histological grade	**Well differentiated**	98 (39.8)
	Moderately differentiated	112 (45.5)
	Poorly differentiated	36 (14.7)
Pattern of invasion	**Pushing**	108 (43.9)
	Infiltrative	138 (56.1)
Depth of invasion	**< 5 mm**	42 (17.1)
	5–10 mm	96 (39.0)
	> 10 mm	108 (43.9)
Tumor thickness	**< 4 mm**	54 (22.0)
	4–10 mm	104 (42.3)
	> 10 mm	88 (35.7)
Keratin pearls	**Present**	142 (57.7)
	Absent	104 (42.3)
Perineural invasion	**Present**	64 (26.0)
	Absent	182 (74.0)

Analysis of the association between clinical parameters and histopathological grade revealed a significant relationship with age, clinical stage, and lymph node status. Among patients younger than 40 years, 28.6% had well-differentiated, 47.6% moderately differentiated, and 23.8% poorly differentiated tumors, compared to 42.0%, 46.4%, and 11.6%, respectively, in the 40–59 years group, and 42.4%, 42.4%, and 15.2% in those aged 60 years or above ($\chi^2 = 8.21$, $p = 0.041$). No significant association was observed with gender, as males and females showed similar distributions of tumor grade ($p = 0.60$). Tumor stage demonstrated a strong association with grade, with early-stage tumors (I–II) more often well differentiated (46.6%) compared to advanced-stage tumors (III–IV), where moderately differentiated histology predominated (50.4%) ($\chi^2 = 12.73$, $p = 0.005$). Similarly, lymph node involvement was significantly associated with tumor grade, as poorly differentiated tumors were more frequent in patients with nodal disease (19.2%) compared to those without (11.8%) ($\chi^2 = 9.84$, $p = 0.021$). (Table 5)

Table 5. Association Between Clinical Parameters and Histopathological Grade of study participants (n=246)

Clinical Parameter	Grade			χ^2 value	p-value
	Well (n=98)	Moderate (n=112)	Severe (n=36)		
Age < 40	12 (28.6%)	20 (47.6%)	10 (23.8%)	8.21	0.041*
Age 40–59	58 (42.0%)	64 (46.4%)	16 (11.6%)		
Age ≥ 60	28 (42.4%)	28 (42.4%)	10 (15.2%)		
Male	62 (39.7%)	72 (46.2%)	22 (14.1%)	1.02	0.60
Female	36 (40.0%)	40 (44.4%)	14 (15.6%)		
Stage I–II	54 (46.6%)	48 (41.4%)	14 (12.0%)	12.73	0.005*
Stage III–IV	44 (34.6%)	64 (50.4%)	22 (15.0%)		
Lymph node absent	68 (44.7%)	66 (43.4%)	18 (11.8%)	9.84	0.021*
Lymph node present	30 (31.9%)	46 (48.9%)	18 (19.2%)		
**Statistically significant*					

Discussion

In this cross-sectional study of 246 Pakistani patients with oral squamous cell carcinoma (OSCC), most patients were middle-aged (mean 51.7 years), there was male predominance (63.4%), the buccal mucosa was the commonest site (41.5%), betel-quid chewing and tobacco use were frequent risk factors, moderately differentiated tumors predominated (45.5%), a majority demonstrated infiltrative invasion and substantial depth/thickness, and more than half presented with advanced

disease (stage III–IV). We also found statistically significant associations between histological grade and patient age, clinical stage, and nodal status. These findings broadly align with several recent regional studies but also show some differences in relative frequencies, which warrant discussion.

Age and gender distribution. The predominance of middle-aged adults and male predominance in our cohort mirrors multiple Pakistani series that report peak incidence in the 4th–6th decades and higher male: female ratios. A study by Anwar et al. 2020 and Yasin et al. 2022 from Karachi reported mean ages in the 40s–50s with male predominance, consistent with our results. The concentration of cases in working-age adults likely reflects the exposure period to carcinogenic habits and delayed presentation patterns observed in the region.[11, 12]

Primary site and risk habits. The predominance of buccal mucosa and tongue in our data is similar to several Pakistani studies where buccal mucosa is commonly affected, especially in communities with prevalent smokeless tobacco and betel-quid habits, while other centers report a higher tongue proportion depending on local habit patterns. Anwar et al. (2020) similarly emphasized smokeless tobacco and betel-quid as major regional risk factors and linked buccal mucosa involvement to these habits; Younas et al. (2023) also reported buccal mucosa and lip predominance in their series. Differences between centers (buccal mucosa vs tongue predominance) likely reflect local variations in specific habits and referral bias to tertiary centers.[10, 11, 13]

Histological grade and patterns. In our hypothetical cohort, moderately differentiated carcinomas were most frequent (45.5%), and well-differentiated tumors formed the next largest group. This distribution is in keeping with several hospital-based studies from Pakistan and nearby regions that commonly report a predominance of well to moderately differentiated tumors rather than a predominance of poorly differentiated lesions. Studies by Yasin et al. (2022) and Irfan et al. (2024) observed similar grade distributions, with poorly differentiated tumors forming a minority. Differences in grading proportions across series may reflect differences in referral patterns, disease stage at presentation, and interobserver grading variation.[12, 14]

Stage at presentation and depth/pattern of invasion. A notable finding in our dataset was the high proportion of advanced stage disease (56.1% stage III–IV) and a large fraction with depth of invasion >10 mm and infiltrative invasion pattern; this echoes the well-documented problem of late presentation in Pakistan. Anwar et al. (2020) similarly reported a high proportion of late-stage presentations at a tertiary center, and other retrospective Pakistani series also describe substantial stage III–IV caseloads. The combination of deep invasion, infiltrative pattern, and advanced stage observed in our cohort helps explain the higher nodal positivity and underscores the prognostic relevance of depth and invasion pattern reported in the literature.[11]

Association of clinicopathological variables. We found statistically significant associations between poorer histological grade and younger age group (<40), advanced clinical stage, and positive nodal status. Several studies from the region report similar clinicopathologic links—particularly the association of higher stage and nodal metastasis with poorer differentiation and aggressive invasion patterns. Yasin et al. (2022) and Irfan et al. (2024) highlight the correlation of adverse histopathologic features with nodal metastasis and poorer clinical outcomes; these observations support our findings that histologic grade and invasion metrics correlate with stage and nodal disease. Differences such as a relatively higher proportion of moderately differentiated tumors in advanced stages in our cohort may be due to sampling and the cross-sectional design rather than longitudinal progression data.[12, 14]

Studies showed comparable themes, male predominance, a preponderance of buccal mucosa in populations with heavy smokeless tobacco use, and frequent late-stage presentation, although the exact percentages vary by population. An Iranian tongue-SCC series reported higher tongue involvement and emphasized site-specific clinicopathologic differences, illustrating how local habits modify the anatomic distribution of disease. Similarly, epidemiologic trend analyses by Babu et al. 2021 emphasized geographic variability in site and grade proportions.These comparisons suggest that while our findings are broadly consistent with regional trends, local social and cultural

practices (tobacco/quid type, quid placement, healthcare access) importantly shape the clinicopathologic profile seen in any particular center. [15, 16]

Possible explanations for divergences. Where our data differ numerically from other reports (for example, slightly higher buccal mucosa percentage or higher proportion with >10 mm depth), plausible reasons include referral bias to tertiary care centers (which tend to receive more advanced cases), differences in habit prevalence in the catchment population, and variability in biopsy sampling or grading criteria. Interobserver variability in histologic grading and differences in how depth/tumor thickness is measured also contribute to between-study heterogeneity. Finally, temporal changes in habit prevalence and public health messaging between study periods could shift the distribution of sites and stages over time.[11, 12]

The concordant themes across studies, high prevalence of preventable risk factors (betel/quids, smokeless tobacco), frequent late presentation, and the prognostic importance of histologic grade, invasion pattern, and depth, underscore the need for targeted public health interventions, improved early-detection efforts, and standardized pathology reporting to better stratify risk and personalize treatment. Incorporating routine, standardized reporting of prognostic histopathologic parameters in pathology reports and increasing primary care/ community awareness about early signs of OSCC could reduce late-stage presentations noted both in our series and in the literature.

Limitations

Our study is hospital-based and cross-sectional, so direct comparisons with population-based incidence or longitudinal outcome data are limited. Interstudy differences in inclusion criteria, grading methods, and referral patterns complicate direct numerical comparisons. Finally, because this report used hypothetical data for the present manuscript draft, future validation using prospectively collected, multi-center data would strengthen generalizability.

Conclusion

Our study highlights that oral squamous cell carcinoma in Pakistan remains strongly linked to preventable lifestyle factors such as betel-quid chewing, smokeless tobacco, and areca nut use, with the buccal mucosa as the most commonly affected site. The predominance of moderately differentiated tumors, coupled with a high frequency of advanced stage presentation, underscores the aggressive nature of the disease and the burden of late diagnosis. The significant associations observed between histological grade, clinical stage, and nodal status emphasize the value of comprehensive clinicopathological assessment in guiding prognosis and treatment. When viewed alongside recent studies from 2020 to 2024, our findings reaffirm the urgent need for community-level preventive strategies, robust awareness campaigns, and standardized pathology reporting to reduce OSCC morbidity and mortality.

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